SERIOUS, POSSIBLY ASSOCIATED AND UNEXPECTED ADVERSE EVENTS
REPORTED FOR HUMAN GENE TRANSFER PROTOCOLS
REPORTING PERIOD: 05/01/01 -- 08/01/01
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
September 2001

Event #	OBA Date	Event Date	Protocol #	Event Description
			9512-138	**A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-β2 Antisense Gene Modified Autologous Tumor Cells.**
3589	04/23/2001	09/15/2000		Subject was prophylactically placed on antibiotic (Keflex) after having been dosed with investigational agent that was presumed contaminated with coagulase-negative Staphylococcus. The subject never exhibited any indications of infection. The event is thought to be a false positive. Retesting of archived investigational agent samples confirmed the absence of any bacterial contamination and validated the suspicion of a false positive result. The attribution of the event was changed to "unrelated to IND agent".
			9611-165	**Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.**
3585	05/17/2001	04/17/2001		Approximately 6 hours post injection, subject complained of shortness of breath. O_2 was administered via nasal cannula. The shortness of breath resolved. Two hours later, the subject developed a fever of 39.2 °C, treated with Tylenol and supplemental oxygen. The following morning, subject's blood pressure was 88/51, and was fever down to 37.5 °C. A bolus of IV fluids was administered. Temperature normalized to 37 °C, blood pressure normalized and there were no further complaints of shortness of breath. The subject was discharged. It was suspected that the shortness of breath was probably due to the subject's history of asthma or possibly related to documented lung metastases. The mild hypotension was believed to be associated to investigational agent.
3619	05/25/2001	05/12/2001		After vaccination, the subject experienced fevers to 41.3 °C, but these resolved within 24 hours and the subject was discharged to home. The subject reported continued fevers, nausea, and malaise at home, but he did not take any medications and symptoms resolved by day 5. The adverse event was considered possibly related to the investigational agent.
3618	05/25/2001	05/15/2001		Subject was admitted with a pruritic, macular-papular rash over the entire body. The rash began two days post vaccination. The subject had previously been vaccinated 18 days before this vaccination. The rash first began around the injection site but became generalized by the 4th day post-vaccination. A new medication had also been started on the day of vaccination and the subject had apparently continued this new medication up to the fifth day post-vaccination. The rash was considered possibly related to the investigational agent vaccination, but the dermatologist felt that the subject's symptoms and history were consistent with a drug rash.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9802-238	**Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina. Sponsor: Berlex Laboratories, Inc.**
3573	05/14/2001	05/07/2001		(see also #3001, #3015). Previous reports outline that the subject received study agent Ad5FGF-4 on 6/29/00. On 9/6/00 subject complained of speech impediment. MRI on 10/13/00 showed a space occupying lesion in the left temporoparietal region of the brain. Unknown if primary or secondary - biopsy should identify. Sponsor indicated that if the tumor is primary, association with investigational agent is unlikely; if tumor is secondary (metastatic), possible association with investigational agent cannot be ruled out. Subject expired from complications secondary to glioblastoma. This particular submission is a notification that this subject expired, exhibiting papilledema secondary to the glioblastoma multiforme. The suspected cause of the event was the left temporoparietal glioblastoma and the event was considered "possibly related" to the investigational agent.
			9902-288	**Phase I Pilot Trial of Adenovirus p53 and Radiotherapy on Non-Small Cell Lung Cancer. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
3571	05/10/2001	05/09/2001		About one month after the subject was removed from the protocol, a CT scan showed a large pericardial effusion and an echocardiogram demonstrated early tamponade. There were no other signs of disease progression. The subject was to have a therapeutic and diagnostic pericardiocentesis. The event was considered possibly related to the administration of the investigational agent Ad-p53.
3622	05/29/2001	05/09/2001		Subject same as in #3571, also experienced Grade 3 recurrent rapid atrial fibrillation while hospitalized. Event was considered possibly related to the investigational agent.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9902-292	**Immunization of Patients with Metastatic Melanoma Using a Recombinant Fowlpox Virus Encoding a GP 100 Peptide Preceded by an Endoplasmic Reticulum Insertion Signal Sequence. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
3545	05/07/2001	01/11/2001		One day post treatment, subject with metastatic melanoma became hypotensive after receiving a dose of the investigational agent. Subject's blood pressure improved following administration of fluids intravenously. PI attributes the hypotension as probably due to investigational agent, Fowlpox/esgp 100.
3548	05/07/2001	03/09/2001		The subject experienced the same hypotensive symptoms with the second cycle of fowlpox/esgp 100 vaccine and IL-2, which again responded to intravenous fluid administration. One day prior to his third cycle he had a CT scan with oral contrast. Prior to the CT scan his creatinine level was normal at 1.0. On the day after the fowlpox/esgp100 dosing, the subject was admitted for administration of the IL-2. During the admission the subject was hypotensive and the creatinine level was 2.1. The IL-2 was not administered. The subject's blood pressure and creatinine normalized with fluid therapy. The investigator reported that the hypotension was probably attributable to the fowlpox/esgp 100, and the creatinine elevation was possibly attributable to the oral contrast agent or the fowlpox/esgp 100. The investigator noted that a few other subjects had developed a hypersensitivity to contrast after receiving IL-2.
3576	05/11/2001	01/11/2001		Same description of events as provided by the sponsor. Additional information submitted by the sponsor indicates that bouts of asymptomatic hypotension resulted after administration of the investigational agent during earlier interventions and in the absence of any high dose IL-2 regimen. The sponsor states that the hypotension attribution should be considered a probable association with the investigational agent whereas the creatinine increase should be considered as a possible association with either the investigational agent, the oral contrast, or both.
3577	05/11/2001	03/09/2001		Same information as provided in #3576.
			9902-294	**A Multicenter, Open-Label, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF-2) Gene Therapy in Refractory Patients with Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures. Sponsor: Vascular Genetics, Inc.**
3762	07/18/2001	05/02/2001		An elderly subject who received pVGI.1(VEGF2) had two skin lesions (from arm and upper chest) removed 15 months after the investigational agent was administered. Both lesions showed squamous cell carcinoma *in situ*. Twenty-four months after the investigational agent, the subject had two skin lesions removed (from opposite arm and one foot). These were also squamous cell carcinoma in situ (Bowen's disease). The margins on all four lesions were negative for malignancy. The Investigator considered these events to be "possibly related" to the investigational agent.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9903-296	**Phase I Trial of Immunotherapy with Adenovirus-Interferon-Gamma (TG1041) in Patients with Malignant Melanoma. Sponsor: Transgene, Inc.**
3668	06/22/2001	03/12/2001		Within 4 hours following investigational agent injection (3rd cycle), subject experienced grade 3 flu-like syndrome with fever, chills, muscle aches in the right leg, nausea, injection site inflammation and mild face flushes. A mild upper respiratory infection with productive cough, right earache, left ear congestion and rhinitis were also noted but believed to be unrelated to the investigational agent. The subject was admitted for observation and treated with Tylenol, potassium chloride and cefepime. The event resolved the next day. Blood and urine cultures were negative. Subject had a similar syndrome about 6 hours after the second injection, but was at home and did not inform the PI until the day of the third injection. This submission details the cytokine changes seen with the flu-like syndrome occurring after the third administration of investigational agent. It was associated with an increase in IFN-γ, β-2 microglobulin and IL-6 and a decrease of TNF-α. The values were back to baseline at 24 hours for IFN-γ and IL-6. The event was judged to be of probable relationship to the administration of the investigational agent TG 1041. The subject had no cytokine increases after 1st injection, but there was some depression of TNF-alpha levels. No testing was performed after the 2nd injection.
			9910-346	**A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization. Sponsor: Parke-Davis Pharmaceutical Research**
3544	05/07/2001	04/25/2001		Subject with a significant history for 3 prior myocardial infarctions and chronic obstructive pulmonary disease received 30 intramyocardial injections of investigational agent. Six hours post-administration, the subject was extubated and subsequently reintubated within 5 hours after developing a respiratory insufficiency. The subject went on to develop cardiac shock, secondary to a myocardial infarction (MI). The subject's condition is stable but the event is ongoing. The PI attributed the MI and subsequent cardiac shock as definitely related to either the procedure, investigational agent or both, while the respiratory insufficiency is considered probably related. The sponsor attributes the MI as possibly associated to the investigational agent and definitely related to the study procedure. The cardiac shock is deemed unlikely related to the investigational agent, but definitely related to the study procedure, and the respiratory insufficiency deemed unlikely related to the investigational agent, but probably related to the study
3580	05/18/2001	05/12/2001		See also #3544. Subject expired 19 days post injection of investigational agent. The cause of death is pending an autopsy.
3643	06/12/2001	05/12/2001		As a result of the myocardial infarction (MI), balloon pump support was initiated and removed 7 days later. The subject became septic on study day 11, the pump support was reinstalled but the subject's condition deteriorated in spite of triple antibiotic therapy. The cause of death was attributed to cardiac shock and possibly sepsis with ensuing multisystem failure. The sepsis was definitely not attributable to the investigational agent. The sponsor considers the cardiac shock and MI definitely related to the study procedure, and the respiratory insufficiency and sepsis possibly related to the study procedure.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9912-360	**Treatment of Patients with Metastatic Melanoma Using Cloned Lymphocytes Following the Administration of a Nonmyeloablative But Lymphocyte Depleting Regimen.**
3559	05/09/2001	04/23/2001		Subject with metastatic melanoma complained of chest congestion 4 days post administration of investigational agent and IL-2. Oxygen saturation levels were 90% on room air and increasing supplemental oxygen requirements led to the subject being semi-electively intubated. A chest X-ray demonstrated a right lower lobe infiltrate with concomitant fever that prompted multiple antibiotic therapy. Subject was also treated for hypotension with IV fluids and briefly with pressors. A bronchoscopy with lavage was shown to be positive for respiratory syncitial virus infection and the subject was treated with Ribavirin inhalation solution therapy. The subject's condition improved and subject was extubated after 6 days. The event is considered possibly associated to a preparative regimen likely to induce lymphopenia and neutropenia. Lung damage and risk of infection are known possible complications and are listed in
			9912-361	**Elicitation of a Cellular Immune Response in Patients with Non-Small Cell Lung Cancer by Immunogenic Tumor Cell Vaccination - A Phase I Study.**
3634	06/05/2001	05/26/2001		Subject with lung cancer received 8 vaccinations of investigational agent over the course of 17 weeks. Five days after the last dose, subject was admitted with generalized edema felt to be related to the development of a large pericardial effusion. The cause of the pericardial effusion was uncertain, but the leading possibilities were extension of the lung cancer to the pericardium or an inflammatory pericarditis. In the later event, the vaccine could have played a role. Follow up information will be forthcoming following pericardial biopsy and fluid analysis.
			0001-369	**A Phase I Study of Vaccination with Lethally Irradiated, Autologous Acute Myeloblastic Leukemia Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor in Patients with Advanced Myelodysplasia or Acute Myelogenous Leukemia.**
3773	07/26/2001	05/14/2001		A CT scan confirmed the occurrence of a lower lobe pneumonia. Subject was released from the hospital 7 days after admission for the pneumonia. Causality of the event was changed to "unlikely related" to the investigational agent.
3772	07/26/2001	05/14/2001		Subject with acute myeloblastic leukemia developed fever, shortness of breath and non-productive cough, and twenty days after the 11th vaccine of the third dosing round of investigational agent was admitted to the hospital for treatment of a lower lobe pneumonia. The event was initially considered as possibly related to the investigational agent pending a subsequent CT scan.

Event #	OBA Date	Event Date	Protocol #	Event Description
			0001-372	**A Phase 1, Single-Dose, Dose-Escalation Study of MiniAdFVIII Vector in Patients with Severe Hemophilia A. Sponsor: GenStar Therapeutics Corporation**
3733	07/11/2001	06/13/2001		Approximately 5 hours after intravenous infusion of investigational agent (Mini-AdFVIII) the subject developed fever, chills, achiness, back pain and headache. The fever peaked at 102.6 °F, approximately 8 hours after investigational agent infusion, and resolved by about 12 hours. The subject, who has a history of multiple spontaneous bleeds, experienced a spontaneous hemarthrosis of the knee on Day 1 post investigational agent infusion, treated in the usual manner with recombinant factor VIII (r-AHF) with resolution of the bleeding event. The subject also experienced elevations in liver enzyme values with ALT peaking on post-infusion Day 7 and AST values peaking on post-infusion Day 7 and transient declines in factor VII levels and platelet counts. All laboratory values returned to baseline by Day 19 and were not considered clinically serious. Event attributions were not addressed in this submission.
			0001-381	**Gene Therapy of Canavan Disease using AAV for Brain Gene Transfer.**
3662	06/21/2001	06/06/2001		Subject with Canavan Disease and a history of seizure disorder developed a fever on day 1 post-administration of the investigational agent. The hospitalization of the subject was extended due to fever (102.7 °F). The fever decreased following treatment with antipyretics. The event is considered "serious" because of the 24 hour extension of hospitalization, and possibly related to the investigational agent. The subject was noted to have mild nasal drainage on post-op day 3 suggestive of a mild upper
			0001-387	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering $AD_{GV}VEGF_{121.10}$ (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease. Sponsor: Parke-Davis Pharmaceutical Research**
3633	06/05/2001	05/26/2001		Subject with history of coronary artery bypass graft and subsequent graft vessel blockage was admitted for recurrence of chest pain. Thallium scan showed anterior, apical and septal ischemia. PI states the event to be possibly related to the investigational agent (Ad-VEGF) on the OBA reporting form, yet considers the attribution as "doubtful" on the accompanying CTC form.

Event #	OBA Date	Event Date	Protocol #	Event Description
			0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 ($AD_{GV}VEGF_{121.10}$) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**
3671	06/27/2001	06/12/2001		At the one week follow-up, the subject complained of swelling of the injected leg. The ankle brachial index was below the baseline value and the swelling was clinically significant. Venous Doppler ultrasound imaging was negative. The event was considered to be probably related to the investigational agent.
3714	07/05/2001	06/12/2001		The sponsor provided new information to indicate that the swelling had begun on day 1 post-injection and that the subject had in fact received the active investigational agent (Ad-VEGF). Both the investigator and the sponsor deemed the event "definitely related" to the administration of the Ad-VEGF.
			0006-402	**Phase I Study to Evaluate the Safety of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma Using Genetically-Modified Autologous CD8+ T Cell Clones.**
3791	07/31/2001	07/30/2001		Within 15 minutes of investigational agent infusion, subject (diagnosed with multiply recurrent metastatic neuroblastoma) developed a new dry cough and a slight facial flushing not associated with respiratory distress, O2 saturation or blood pressure fluctuation. Several minutes later, the subject complained of non-specific lower back and hip pain. The infusion was stopped and the pain was treated with IV Demerol after which the subject developed a severe itching involving scalp, arms and feet without changes in the skin. Benadryl was given to alleviate the itching. Pain returned after 6.5 hours to a lesser degree along with nausea, headache and reappearance of the cough prompting another set dose of Benadryl / Demerol. All symptoms resolved spontaneously within 12 hours. The subject was noted to be lymphopenic. The PI believes the following events are attributable to administration of the investigational agent: grade 2 neuropathic pain, grade 2 pruritis, grade 1 cough, and grade 1 nausea (grade 1 cough has been observed with other subjects in this trial).
3798	08/01/2001	07/30/2001		The PI provided a possible indication of the suspected cause of the events: "Unclear, potentially T-cell effect of L1-CAM+ pain nerves (similar to anti-GD2 antibody)".
			0006-403	**A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina. Sponsor: Berlex Laboratories**
3783	07/27/2001	01/10/2001		Previously, in #3299 and #3381, it was reported that a subject developed positive test results for Hepatitis C, but samples of the final product, the master cell bank, and reserve samples of the bulk and the harvest used to prepare the final product had all tested negative for Hepatitis C virus. This new submission reports that a second independent lab retested the investigational product for HCV by rtPCR and again the result was negative. Therefore, the causality of the adverse event in submission #3299 was changed to "unlikely related" to investigational agent.

Event #	OBA Date	Event Date	Protocol #	Event Description
			0006-405	**A Phase I Study of Sequential Vaccinations with Fowlpox-CEA (6D)-TRICOM (B7.1/ICAM-1/LFA-3) Alone, OR in Combination with Vaccinia-CEA-(6D)-TRICOM, and the Role of GM-CSF, in Patients with CEA Expressing Carcinomas.**
3629	06/04/2001	05/31/2001		Subject with CEA-expressing carcinoma and receiving intramuscular thigh injections of investigational agent on a 28 day cycle, expired after back surgery. The cause of death is unknown at this time. The PI considers the event as not related to the investigational agent.
			0007-407	**A Phase I Double-blind, Placebo-Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention. Sponsor: Genzyme Corporation**
3615	05/24/2001	05/09/2001		During a routine office visit twenty five days after investigational agent administration, the subject developed acute neurologic deficits which were transient in nature. Five weeks after investigational agent administration the subject was admitted for preoperative screening for a planned endarterectomy. This particular submission notes that at that time of preoperative screening, the subject reported having had shortness of breath for 4-5 days when lying on the left side. A chest X-ray indicated a right pleural effusion and the fluid was withdrawn. The subject recovered, was discharged and the endarterectomy postponed. The event (pleural effusion with shortness of breath) was considered possibly related to investigational agent, as it occurred later in the post-operative course of the study.